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Patient-Reported Outcomes for Acute Graft-versus-Host Disease Prevention and Treatment Trials

Stephanie J. Lee,[1] *Loretta A. Williams*[2]

Patient-reported outcomes (PROs) such as health-related quality of life, functional status, and symptom burden have been recognized by the U.S. Food and Drug Administration (FDA) as legitimate measures of clinical benefit for sponsors seeking drug approval. However, in practice, very few agents have been approved based on these endpoints. Successful use of PROs in registration trials requires rigorous methods to overcome numerous logistic and analytic barriers. Acute graft-versus-host disease (aGVHD) is associated with high morbidity and mortality, and its prevention and treatment are the goals of many clinical trials in the hematopoietic cell transplantation (HCT) research community. This article summarizes issues to be considered in the use of PROs as endpoints in aGVHD prevention and treatment trials.

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INTRODUCTION

Patient-reported outcomes (PROs) refer to health-related quality of life, functional status, and symptom burden as perceived and reported by patients. For example, symptoms are subjective phenomena reported by patients that indicate a change in normal functioning, sensation, or appearance because of disease [1]. Patient-reported measurement tools include surveys, interviews, or patient diaries. These instruments try to capture what people actually experience with a treatment approach. Patient-reported measures are complementary to physical exam findings and laboratory testing, and are the primary source for much of the clinician-reported symptom information in the chart. For example, patient self-report is the most direct means of capturing severity of nausea, pain, and anorexia, and the only way to capture information about fatigue and patient-perceived illness impact. In recognition of this reality, the Common Terminology Criteria for Adverse Events is undergoing revision to include PRO items for symptom severity [2]. In summary, PROs reflect the patient's personal experience with disease and treatment.

Acute graft-versus-host disease (aGVHD) primarily involves the skin as an erythematous rash, the liver as a cholestatic or hepatitic process, or the gastrointestinal (GI) system with nausea, vomiting, diarrhea, and abdominal pain. Initial treatment for aGVHD includes corticosteroids, with other immunosuppressive agents added as needed. If symptoms or side effects are moderate to severe, patients may require hospitalization for hydration, nutritional support, intravenous delivery of medications, monitoring, treatment of infections, and other supportive care. Both the aGVHD disease process and the effects of treatments used to prevent or treat GVHD may affect PROs.

In May 2009, the U.S. Food and Drug Administration (FDA), in collaboration with several National Institutes of Health (National Heart, Lung and Blood Institute, National Cancer Institute, and National Institute of Allergy and Infectious Diseases), the Center for International Blood and Marrow Transplant Research (CIBMTR), and the American Society of Blood and Marrow Transplantation (ASBMT) convened a meeting to discuss endpoints in aGVHD trials, particularly with regard to the FDA approval process. This article summarizes the discussion about the role of PROs in trial design and interpretation based on 4 questions posed by the conference organizers.

From the [1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; and [2]Department of Symptom Research, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

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Correspondence and reprint requests: Stephanie J. Lee, MD, MPH, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, N5-290, Seattle, WA 98109 (e-mail: sjlee@fhcrc.org).

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WHAT ARE THE REQUIREMENTS FOR PROS TO BE PRIMARY OR SUPPORTIVE ENDPOINTS?

The FDA requires evidence that treatments provide "clinical benefit" defined functionally as "living longer or living better" before it will consider drug approval. Draft guidance from the FDA states that the amount and kind of PRO evidence to support a labeling claim is the same as that required for any other labeling claim [3]. Patient-reported endpoints may refer to simple concepts, such as single symptoms (eg, pain or nausea) or complex concepts, such as improvement in functioning (eg, working) or psychologic state (eg, mood). Evidence of improvement in simple PRO endpoints is not recognized for complex claims such as improved health-related quality of life. Although it may seem self-evident that decreasing nausea or diarrhea would lead to better quality of life, a sponsor needs to show actual effects on the claim of improved quality of life. The draft guidance also provides insights into the FDA's opinion about several other issues in PRO assessment and analysis such as susceptibility to bias. For example, the guidance notes that cognitive biases may affect patient responses so PROs are considered unreliable in unblinded studies. PRO instruments should capture current status and actual functioning. Recall over more than a short period of time or asking patients to estimate what they may be able to accomplish is subject to substantial bias. The guidance also provides practical advice for sponsors designing trials. Because missing data often compromise analytic plans, reasons for missing data should be recorded during the trial so they can inform the subsequent analysis.

Similar to the use of a new diagnostic tool, the FDA needs to certify a PRO tool to ensure that it is sufficiently validated to support the intended claim in the target population. A previously validated instrument that is modified in any way is considered a different instrument. If the study population differs substantially from the population in which the instrument was validated, the validation may need to be repeated to ensure psychometric integrity. The FDA may choose to review the instrument development and validation process in detail. For example, the FDA may ask to review the process of instrument creation including patient interviews and focus group transcripts, cognitive debriefing procedures, and readability tests. The FDA may evaluate the text of the questions and the response options offered to assess construct validity and ensure absence of ceiling or floor effects. They will determine whether the recall period is appropriate for the study, and evaluate the instrument's psychometric properties including reliability, validity, sensitivity to change, and clinically meaningful differences. Finally, they will review the planned study procedures to ensure accurate data capture, check instrument formatting, and review planned methods of data collection to make sure that results will be considered accurate at the conclusion of the trial.

WHAT CHALLENGES WILL BE ENCOUNTERED, ESPECIALLY FOR aGVHD TRIALS?

There are a number of general challenges to use of PROs as endpoints in clinical trials. First, it is notoriously difficult to collect complete PRO data. PROs are not available retrospectively or from other surrogate sources. Collection of PROs requires active patient cooperation, which is difficult although not impossible to achieve when patients are very ill. For example, Wang et al. [4] reported only 1.7% missing PRO data in a group of 30 patients who completed the M.D. Anderson Symptom Inventory (MDASI) twice weekly during the first 30 inpatient days after allogeneic HCT. Outpatients and those obtaining care in multiple health care settings offer different data collection challenges. Regardless of the setting of a clinical trial, a data collection structure must be put in place that is committed and able to collect all data as completely as possible. Many new technologies, such as interactive voice response systems and Web-based applications, are making collection of PRO data across settings easier and more complete.

Frequency and timing of PRO assessments during aGVHD trials may be critical in detecting a difference in PRO endpoints. Symptoms from aGVHD may begin several days before the diagnosis of disease and worsen until several days after the initiation of effective therapy [5]. Symptoms may then decline rapidly in responding patients after initiation of effective therapy, so an assessment at 100 days or 6 months may miss important differences.

Different survey instruments are often required for children or non-English-speaking patients, increasing trial costs, and decreasing sample size, because often these patients are analyzed as separate subsets. Perhaps the greatest challenge is the fact that PRO tools are clearly intended for research, and currently, separate mechanisms must be established for their collection. Physicians cannot just order PRO measurement as they can a clinical test, contributing to the perception that these are "extra" tasks and expendable because they often do not directly contribute to patient care. Although low-cost data collection options such as telephone and computer technology are being developed, these are not widely used yet [6,7]. A notable exception is the assessment of patient-reported pain severity, which has become routine in hospitals and clinics since being mandated by the Joint Commission on the Accreditation of Healthcare Organizations in 2001 [8],